Food and Drug Administration

Center for Drug Evaluation and Research

Division of Transplant and Ophthalmology Products

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting Briefing Package

for

Ocriplasmin Intravitreal Injection, 2.5 mg/mL

Proposed Indication:
Treatment of symptomatic vitreomacular adhesion including macular hole

July 26, 2012

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Product Information

Proposed Proprietary Name:	Jetrea
Established name:	ocriplasmin
Sponsor:	ThromboGenics Inc. 101 Wood Avenue South, 6th Floor Iselin, NJ 08830
Pharmacologic Category	human plasmin; new molecular entity
Proposed Indication	for the treatment of treatment of symptomatic vitreomacular adhesion including macular hole
Dosage Form and Route of Administration	intravitreal injection

Ocriplasmin (also referred to as microplasmin) is a recombinant truncated form of human plasmin obtained from miroplasminogen produced in a *Pichia pasoris* expression system by recombinant DNA technology with a molecular weight of 27.2kDA.

The drug product is a sterile, clear and colorless solution with no preservatives in a single use glass vial containing 0.5mg of ocriplasmin in 0.4 ml (1.25 mg/mL) solution for intravitreal injection after dilution with 0.9% (w/v) sodium chloride solution. The intended dose is 0.1 ml of the diluted ocriplasmin..

Ocriplasmin was developed for the treatment of vitreomacular adhesion (VMA). The goal of therapy for symptomatic VMA including macular hole is to relieve tractional effects on the macula with subsequent functional improvement. Ocriplasmin contains serine protease activity and is shown to cleave both physiological substrates (such as fibronectin, fibrinogen, collagen, laminin, gelatin, ocriplasmin etc) as well as synthetic peptide substrates (such as S-2403 and S-2444). Following intravitreal administration, the proteolytic activity of ocriplasmin is purported to help in dissolution of the vitreal matrix proteins at the abnormal vitreoretinal interface focal points thereby resolving or reducing the complications associated with VMA.

Tables of Currently Available Treatments for Proposed Indications

There are no pharmacological treatments for symptomatic VMA. The only current treatment for this condition is surgery (vitrectomy).

Chemistry Manufacturing and Controls

The study drug contained 0.75mL of study drug (1.875mg ocriplasmin). The placebo had the same components and concentrations of the study drug with exception of the ocriplasmin.

Components	Concentration	Function
Microplasmin	2.5mg/mL	Active Ingredient
Mannitol	3.75mg/mL	Stabilizer
Citric Acid Monohydrate	1.051mg/mL	Buffer
Water	1mL	Solvent

Source: Table 2 Applicant's Clinical Overview

Tables of Studies/Clinical Trials

Study ID	Design / Control / Indication	Route and Regimen	Total Enrolment (Planned / Actual)
UNCONTROLLED STUDIES			
TG-MV-001	Phase 2 multicenter, open-label, non-controlled 6-month trial with ascending dose / exposure time in 6 sequential cohorts in patients with VMT maculopathy	Single intravitreal injection of ocriplasmin Dose / time before vitrectomy: 25µg/1h; 25µg/24h; 25µg/7d; 50µg/24h; 75µg/24h or 125µg/24h	60/61[a]
TG-MV-010	Phase 2 single center, ascending-exposure time 6-week pharmacokinetic trial prior to pars plana vitrectomy	Single intravitreal injection of ocriplasmin Dose / time before vitrectomy: 125µg/5-30min; 125µg/31-60min; 125µg/2-4h; 125µg/24h; 125µg/7d; no ocriplasmin treatment	36/38
CONTROLLED STUDIES			
TG-MV-002	Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding 12-month study in patients with diabetic macular edema	Single intravitreal injection of ocriplasmin (25µg, 75µg or 125µg) or sham injection	60/51
TG-MV-003	Phase 2 multicenter, randomized, placebo-controlled, double-masked, parallel-group, dose-ranging 6-month study in patients undergoing vitrectomy for non-proliferative vitreoretinal disease	Single intravitreal injection of ocriplasmin (25µg, 75µg or 125µg) or placebo	120/125

TG-MV-004	Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding 6-month trial in patients with VMT	Single intravitreal injection of ocriplasmin (75µg, 125µg or 175µg) or sham injection per cohort[b]	60/61
TG-MV-006	Phase 3 multicenter, randomized, placebo-controlled, double-masked 6-month study in patients with symptomatic VMA (i.e. focal VMA leading to symptoms)	Single intravitreal injection of ocriplasmin 125µg or placebo	320/326
TG-MV-007	Phase 3 multicenter, randomized, placebo-controlled, double-masked 6-month study in patients with symptomatic VMA (i.e. focal VMA leading to symptoms)	Single intravitreal injection of ocriplasmin 125µg or placebo	320/326

Source: Table 1 of the Applicant's Summary of Safety

Individual Studies/Clinical Trials

The safety and efficacy of ocriplasmin for the treatment of VMA was evaluated in two phase 3 trials (TG-MV-006 and TG-MV-007). Both trials were multicenter, randomized, placebo-controlled, double-masked, 6 month studies that investigated the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in patients with symptomatic VMA. The two trials were identical in design (except for allocation ratio of 2:1 in TG-MV-006 and 3:1 in TG-MV-007) and conduct (except for geography: TG-MV-006 conducted in the United States and TG-MV-007 conducted in the European Union and the US.

Clinical Protocol – Studies TG-MV-006 and TG-MV-007

Primary objective: To evaluate the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg dose in subjects with focal vitreomacular adhesion.

Trial design: Multicenter, randomized, placebo controlled, double-masked, trial in which subjects were randomized to either ocriplasmin or placebo intravitreal injection.

If at any point after 4 weeks from time of study drug injection, the underlying condition had not improve (i.e., the adhesion has not been relieved), the Investigator could proceed to vitrectomy at his/her discretion. Additionally, if before this time, the BCVA in the study eye worsened by > 2 lines, or the underlying condition worsened, the Investigator could proceed to vitrectomy at his/her discretion.

Sample Size: 326 subjects/study

VMA status was categorized by the Central Reading Center (CRC) using 1 of 7 categories.

0	1	2	3	4	5	6	7
No visible vitreous separation	Vitreous attached from fovea to ON; separated elsewhere	Vitreous attached at fovea and ON and separated between; may be separated outside	Vitreous attached only at ON or at ON and elsewhere, but not attached at fovea	Vitreous attached only at Fovea	Vitreous visible with complete separation and no attachment	Vitreous separation visible somewhere but unable to determine state of separation	Unable to determine state of separation

Focal VMA was defined by 3 of the 7 categories:

- Vitreous attached from fovea to optic nerve separated elsewhere
- Vitreous attached at fovea and optic nerve and separated between; may be separated outside
- Vitreous attached only at fovea

Inclusion Criteria:

- Male or female subjects aged ≥ 18
- Presence of focal vitreomacular adhesion (i.e., central vitreal adhesion within 6mm optical coherence tomography (OCT) field surrounded by elevation of the posterior vitreous cortex) that in the opinion of the Investigator is related to decreased visual function (such as metamorphopsia, decreased visual acuity, or other visual complaint)
- BCVA of 20/25 or worse in study eye
- BCVA of 20/800 or better in the non-study eye
- Written informed consent obtained from the subject prior to inclusion in the trial

Exclusion Criteria:

- Any evidence of proliferative retinopathy (including proliferative diabetic retinopathy (PDR) or other ischemic retinopathies involving vitreoretinal vascular proliferation) or exudative AMD or retinal vein occlusion in the study eye
- Subjects with any vitreous hemorrhage or any other vitreous opacification which precludes either of the following: visualization of the posterior pole by visual inspection OR adequate assessment of the macula by either OCT and/or fluorescein angiogram in the study eye
- Subjects with macular hole diameter > 400 μm in the study eye
- Aphakia in the study eye
- High myopia (more than 8D) in study eye (unless prior cataract extraction or refractive surgery that makes refraction assessment unreliable for myopia severity approximation, in which case axial length >28 mm is an exclusion).
- Subjects with history of rhegmatogenous retinal detachment in either eye
- Subjects who have had ocular surgery, laser photocoagulation treatment, or intravitreal injection(s) in the study eye in the prior three months
- Subjects who have had laser photocoagulation to the macula in the study eye at any time
- Subjects with pseudo-exfoliation, Marfan's syndrome, phacodenesis or any other finding in the investigator's opinion suggesting lens/zonular instability

- Subjects who have had a vitrectomy in the study eye at any time.
- Subjects with uncontrolled glaucoma in the study eye (defined as intraocular pressure ≥ 26 mm Hg in spite of treatment with anti-glaucoma medication)
- Subjects who are pregnant or of child-bearing potential not utilizing an acceptable form of contraception. Acceptable methods of birth control include intrauterine device, oral, implanted, or injected contraceptives, and barrier methods with spermicide.
- Subjects who, in the Investigators view, will not complete all visits and investigations
- Subjects who have participated in an investigational drug trial within the past 30 days
- Subjects who have previously participated in this trial

Primary Efficacy Endpoint

- Proportion of subjects with nonsurgical resolution of focal vitreomacular adhesion at day 28, as determined by masked Central Reading Center (CRC) OCT evaluation. Any patients that had creation of an anatomical defect (i.e., retinal hole, retinal detachment) that resulted in loss of vision or that required additional intervention were not counted as successes on this primary endpoint.

Secondary Efficacy Endpoint

- Proportion of subjects with total posterior vitreous detachment (PVD) at day 28, as determined by masked investigator assessment of B-scan ultrasound.

Exploratory Endpoints

- Proportion of subjects not requiring vitrectomy
- Proportion of macular holes that close without vitrectomy as determined by CRC
- Achievement of ≥ 2 and ≥ 3 lines improvement on the ETDRS chart in Best Corrected Visual Acuity (BCVA) without need for vitrectomy
- Improvement in BCVA
- Improvement in VFQ-25

Safety Endpoints

Post-injection complications (including adverse events, worsening visual acuity, worsening macular edema, vitreous hemorrhage, retinal tear or detachments, increase in ocular inflammation and IOP increases)

Study Schedule

This was a 6 month study with a total of 7 visits: Baseline, Injection Day (Day 0), Post-Injection Day 7, Post-Injection Day 14, Post-Injection Day 28, Post-Injection Month 3 and Post-Injection Month 6.

	Baseline	Injection Day	Post-Injection Day 7	Post-Injection Day 14	Post-Injection Day 28	Post-Injection Month 3	Post-Injection Month 6
Visit Number	**V #1**	**V #2**	**V #3**	**V #4**	**V #5**	**V #6**	**V #7**
Visit Day *(visit window)*	**BL** [a]	**0**	**7** *(± 2d)*	**14** *(±3d)*	**28** *(± 3d)*	**90** *(± 1w)*	**180** *(±2w)*
Assessments							
Consent	X						
Demography, medical and ocular history	X						
Full ophthalmologic exam [b, c]	X	X	X	X	X	X	X
Pregnancy test [d]	X						
Study drug / placebo injection		X [e]					
B-scan ultrasound [c]	X	X [f]	X	X	X [g]	X [g]	X [g]
OCT [c]	X	X [f]	X	X	X	X	X
VFQ-25	X						X
Fundus Photography [c]	X						X
Fluorescein Angiogram [h]	X						X
AE/SAE reporting		X	X	X	X	X	X

[a] Baseline visit had to be performed within 2 weeks of Visit 2. At the discretion of the Investigator, Visit 1 and Visit 2 could have been combined.

[b] Full ophthalmologic exam included: vision with ETDRS chart, manifest refraction, intraocular pressure, slit-lamp examination and dilated fundus examination. The same slit-lamp machine and lighting conditions were used across study visits for a given subject.

[c] At Baseline, full ophthalmologic exam, B-scan ultrasound, OCT and fundus photography were performed in both eyes; at other study visits, these exams were performed only in study eye.

[d] Was performed in non-menopausal female subjects.

[e] Post-injection, IOP measurement and indirect ophthalmologic examination was performed by the Investigator to exclude retinal non-perfusion or other complications.

[f] If Baseline examination was performed >48 hrs prior to injection, B-scan ultrasound and OCT examination had to be repeated in the study eye.

[g] If total PVD NOT present at prior 2 consecutive visits, then B-Scan ultrasound was performed in the study eye.

[h] FA was performed in both eyes at Baseline visit, and repeated in study eye at Visit 7.

Abbreviations used – Optical Coherence Tomography (OCT), Visual Function Questionnaire (VFQ), Adverse Event (AE), Serious Adverse Event (SAE), Early Treatment Diabetic Retinopathy Study (ETDRS)

Source: Table 3 of the Applicant's Clinical Study Report for Study TG-MV-006

Analysis sets

Safety Set
Consisted of all subjects who received treatment with study drug (ocriplasmin or placebo). The Safety Set was the primary population for all safety analyses.

Full Analysis Set (FAS)
The FAS included all randomized subjects who received treatment with study drug (ocriplasmin and placebo). The FAS was the primary population for all analyses of Baseline/demographic and efficacy data.

Modified Full Analysis Set (FAS)
Defined as all randomized subjects who received treatment with study drug and had symptomatic focal VMA to begin with at Baseline as determined by masked Central Reading Center OCT evaluation.

Per-Protocol Set
The Per-Protocol Set included the FAS excluding subjects where a deviation was of sufficient concern to warrant exclusion.

	TG-MV-006[a]			**TG-MV-007**		
Data Set	**Placebo**	**Ocriplasmin**	**Total**	**Placebo**	**Ocriplasmin**	**Total**
Patients randomized (N)	107	219	326	81	245	326
Full Analysis Set (n, %)	107 (100)	219 (100)	326 (100)	81 (100)	245 (100)	326 (100)
Modified Full Analysis Set (n, %)	99 (92.5)	207 (94.5)	306 (93.9)	77 (95.1)	233 (95.1)	310 (95.1)
Per-Protocol Set (n, %)	94 (87.9)	189 (86.3)	283 (86.8)	71 (87.7)	214 (87.3)	285 (87.4)

Source: Table 3 of the Applicant's Summary of Clinical Efficacy
One patient (Patient 631002) inadvertently received ocriplasmin instead of placebo. Since patients in the Full Analysis Set were analyzed according to the intent-to-treat principle, this patient was counted in the placebo group for the analysis of efficacy

Efficacy Summary

Indication

The indication being sought by the applicant for ocriplasmin is for the treatment of symptomatic vitreomacular adhesion including macular hole.

Demographics

Characteristic	TG-MV-006			TG-MV-007			Integrated Studies		
	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)	Placebo (N=188)	Ocriplasmin (N=464)	Total (N=652)
Gender, n (%)									
Male	48 (44.9)	71 (32.4)	119 (36.5)	25 (30.9)	79 (32.2)	104 (31.9)	73 (38.8)	150 (32.3)	223 (34.2)
Female	59 (55.1)	148 (67.6)*	207 (63.5)	56 (69.1)	166 (67.8)	222 (68.1)	115 (61.2)	314 (67.7)	429 (65.8)
Age (yrs)									
Mean (SD)	71.1 (10.04)	71.5 (10.25)	71.3 (10.17)	70.2 (10.85)	72.6 (7.56)	72.0 (8.54)	70.7 (10.38)	72.1 (8.94)	71.7 (9.39)
Median	70.0	72.0	71.0	72.0	73.0	73.0	71.0	72.0	72.0
Min, max	24, 96	18, 93	18, 96	32, 97	23, 89	23, 97	24, 97	18, 93	18, 97
Race, n (%)									
White	97 (90.7)	195 (89.0)	292 (89.6)	77 (95.1)	233 (95.1)	310 (95.1)	174 (92.6)	428 (92.2)	602 (92.3)
Black	4 (3.7)	13 (5.9)	17 (5.2)	2 (2.5)	10 (4.1)	12 (3.7)	6 (3.2)	23 (5.0)	29 (4.4)
Asian	2 (1.9)	6 (2.7)	8 (2.5)	2 (2.5)	2 (0.8)	4 (1.2)	4 (2.1)	8 (1.7)	12 (1.8)
Other	4 (3.7)	5 (2.3)	9 (2.8)	0	0	0	4 (2.1)	5 (1.1)	9 (1.4)
Ethnicity, n (%)									
Non-Hispanic (USA)	98 (91.6)	204 (93.2)	302 (92.6)	32 (39.5)	103 (42.0)	135 (41.4)	130 (69.1)	307 (66.2)	437 (67.0)
Hispanic (USA)	9 (8.4)	15 (6.8)	24 (7.4)	4 (4.9)	8 (3.3)	12 (3.7)	13 (6.9)	23 (5.0)	36 (5.5)
Not specified (non-USA)	0	0	0	45 (55.6)	134 (54.7)	179 (54.9)	45 (23.9)	134 (28.9)	179 (27.5)
Baseline Diagnosis, n (%)[a]									
FTMH	32 (29.9)	57 (26.0)	89 (27.3)	15 (18.5)	49 (20.0)	64 (19.6)	47 (25.0)	106 (22.8)	153 (23.5)
VMT (including DR)	75 (70.0)	162 (74.0)	237 (72.7)	66 (81.5)	196 (80.0)	262 (80.4)	141 (75.0)	358 (77.2)	499 (76.5)

Characteristic	TG-MV-006			TG-MV-007			Integrated Studies		
	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)	Placebo (N=188)	Ocriplasmin (N=464)	Total (N=652)
Baseline Ocular Characteristics, n (%)[b]									
ERM	35 (32.7)	86 (39.3)	121 (37.1)	33 (40.7)	98 (40.0)	131 (40.2)	68 (36.2)	184 (39.7)	252 (38.7)
Pseudophakic	29 (27.1)	91 (41.6)*	120 (36.8)	24 (29.6)	81 (33.1)	105 (32.2)	53 (28.2)	172 (37.1)*	225 (34.5)
DR	7 (6.5)	12 (5.5)	19 (5.8)	8 (9.9)	18 (7.3)	26 (8.0)	15 (8.0)	30 (6.5)	45 (6.9)
Type (Diameter) of Focal VMA, n/N (%)[c]									
> 1500µm	19/99 (19.2)	47/207 (22.7)	66/306 (21.6)	22/77 (28.6)	55/233 (23.6)	77/310 (24.8)	41/176 (23.3)	102/440 (23.2)	143/616 (23.2)
≤ 1500µm	74/99 (74.7)	145/207 (70.0)	219/306 (71.6)	49/77 (63.6)	169/233 (72.5)	218/310 (70.3)	123/176 (69.9)	314/440 (71.4)	437/616 (70.9)
Could not determine	6/99 (6.1)	15/207 (7.2)	21/306 (6.9)	6/77 (7.8)	9/233 (3.9)	15/310 (4.8)	12/176 (6.8)	24/440 (5.5)	36/616 (5.8)
Expected Need for Vitrectomy, n (%)[d]									
Yes	85 (79.4)	174 (79.5)	259 (79.4)	67 (82.7)	222 (90.6)	289 (88.7)	152 (80.9)	396 (85.3)	548 (84.0)
No	22 (20.6)	44 (20.1)	66 (20.2)	14 (17.3)	23 (9.4)	37 (11.3)	36 (19.1)	67 (14.4)	103 (15.8)
Missing	0	1 (0.5)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Total PVD at Baseline, n (%)									
Yes	0	1 (0.5)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
No	107 (100.0)	218 (99.5)	325 (99.7)	81 (100.0)	245 (100.0)	326 (100.0)	188 (100.0)	463 (99.8)	651 (99.8)

Characteristic	TG-MV-006			TG-MV-007			Integrated Studies		
	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)	Placebo (N=188)	Ocriplasmin (N=464)	Total (N=652)
BCVA (Letter Score)									
Mean (SD)	65.3 (9.83)	64.5 (10.86)	64.8 (10.53)	64.9 (11.58)	63.4 (13.69)	63.8 (13.20)	65.1 (10.59)	63.9 (12.43)	64.3 (11.94)
Median	67.0	67.0	67.0	66.5	67.0	67.0	67.0	67.0	67.0
Min, max	38, 82	20, 85	20, 85	9, 82	8, 88	8, 88	9, 82	8, 88	8, 88

Reference: Table 1.2.1, Table 2.2.1.1, Table 2.2.2.1 and Table 2.2.2.2, Module 5.3.5.3
BCVA=best corrected visual acuity; DR=diabetic retinopathy; ERM=epiretinal membrane; FTMH=full thickness macular hole; PVD=posterior vitreous detachment; SD=standard deviation; USA=United States of America; VMA=vitreomacular adhesion; VMT=vitreomacular traction
* denotes a statistically significant difference between treatment groups.
[a] Based on CRC review of pre-treatment OCT. All cases other than FTMH were considered to be VMT.
[b] Patients could have had > 1 baseline ocular characteristic.
[c] Percentages are based on total number of patients in the Modified Full Analysis Set.
[d] Yes / no answer for the question asked of the investigator prior to randomization: "If no improvement in this patient's condition, do you think you would proceed to vitrectomy?"

Source: Table 4 of the Applicant's Summary of Clinical Efficacy

Subject Disposition

Patient Disposition (TG-MV-006, TG-MV-007 and Integrated Studies)

	TG-MV-006			TG-MV-007		
	Placebo	**Ocriplasmin**	**Total**	**Placebo**	**Ocriplasmin**	**Total**
Patients randomized (N)	107	219	326	81	245	326
Completed study, n (%)	98 (91.6)	200 (91.3)	298 (91.4)	74 (91.4)	235 (95.9)	309 (94.8)
Discontinued from study, n (%)	9 (8.4)	19 (8.7)	28 (8.6)	7 (8.6)	10 (4.1)	17 (5.2)
Adverse event	2 (1.9)	2 (0.9)	4 (1.2)	0	2 (0.8)a	2 (0.6)
Investigator decision	0	0	0	1 (1.2)	0	1 (0.3)
Withdrew consent	4 (3.7)	8 (3.7)	12 (3.7)	4 (4.9)	5 (2.0)	9 (2.8)
Lost to follow-up	3 (2.8)	6 (2.7)	9 (2.8)	2 (2.5)	2 (0.8)	4 (1.2)
Death	0	3 (1.4)	3 (0.9)	0	1 (0.4)	1 (0.3)

Note: One patient (Patient 631002, TG-MV-006) was randomized to placebo but was inadvertently treated with ocriplasmin instead of placebo.
a One patient (Patient 721008, TG-MV-007) discontinued due to metastatic brain cancer and subsequently died. This patient is not counted as discontinuing due to death in this table.
Source: Table 4 of the Applicant's Clincal Overview

Efficacy Endpoint (s)

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients with non-surgical resolution of focal VMA at Day 28 post-injection as determined by masked CRC OCT evaluation. Any patients who had creation of an anatomical defect (i.e. retinal break, retinal detachment) that resulted in loss of vision or that required additional intervention were not counted as successes for the primary endpoint. The Full Analysis Set was the primary population for all analyses of baseline/demographic and efficacy data. Missing data was imputed using the last observation carried forward (LOCF) approach. The treatment groups were compared using Fisher's exact test. The two-sided 95% CIs for the difference between the 2 groups were also calculated. For the integrated analysis of the two studies, differences between treatments were evaluated using Cochran-Mantel-Haenszel test, stratified by study.

Proportion of Patients with VMA Resolution in the Study Eye at Day 28 without Creation of an Anatomical Defect (TG-MV-006, TG-MV-007 and Integrated Studies: Full Analysis Set, Modified Full Analysis Set and Per-Protocol Set)

	TG-MV-006				TG-MV-007			
	PL	Ocriplasmin	Difference (95% CI)[a]	p-value[b]	PL	Ocriplasmin	Difference (95% CI)[a]	p-value[b]
Full Analysis Set								
N	107	219			81	245		
n (%)	14 (13.1)	61 (27.9)	14.8(6.0,23.5)	0.003	5 (6.2)	62 (25.3)	19.1 (11.6,26.7)	<0.001
Modified Full Analysis Set								
N	99	207			77	233		
n (%)	14 (14.1)	61 (29.5)	15.3 (6.1,24.6)	0.004	5 (6.5)	62 (26.6)	20.1 (12.2,28.0)	<0.001
Per-Protocol Set								
N	94	189			71	214		
n (%)	14 (14.9)	58 (30.7)	15.8 (6.0,25.5)	0.004	4 (5.6)	56 (26.2)	20.5 (12.6,28.5)	<0.001

Source: Table 6 of the Applicant's Summary of Clinical Efficacy

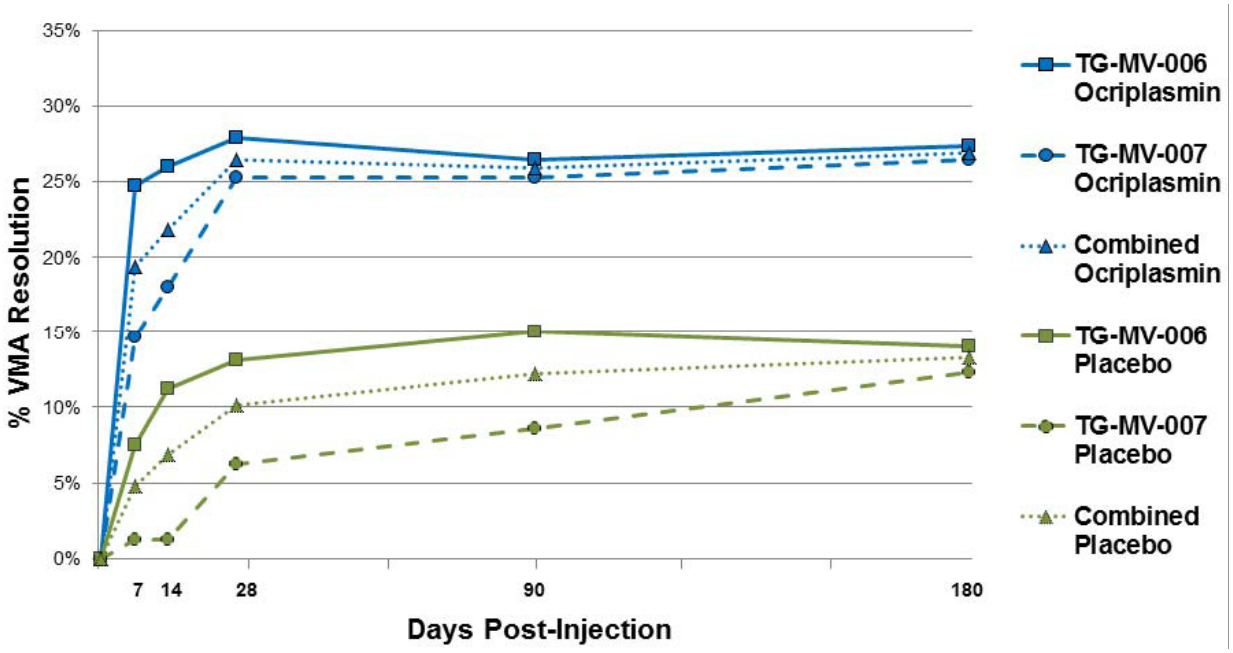
CI=confidence interval; PL=placebo; VMA=vitreomacular adhesion

[a] The (absolute) difference and CIs between treatment groups are based on the proportion of successes.

[b] For individual studies, p-value is from Fisher's exact test, comparing placebo and ocriplasmin. For pooled studies, p-value is from Cochran-Mantel-Haenszel test comparing placebo and ocriplasmin, stratified by study.

Ocriplasmin is statistically superior to placebo in both of the phase 3 trials for all of the analysis sets. While the drug response rate appears consistent in both trials, the placebo event rate is twice as high in Study 006 compared to 007. The applicant postulates that this could have resulted from factors such as more patients with macular holes, less epiretinal membrane cases and higher proportion of patients with VMA diameter ≤ 1500µm in study 006. Some studies have shown that spontaneous resolution of VMA occurs more often in patients with VMA diameter ≤ 1500µm and in those without associated ERM; however, this effect should also be seen in the drug group not just in the placebo group. While not statistically significant, it is unclear why there is such a large discrepancy in the placebo rates in these two trials.

Proportion of Patients with VMA Resolution in the Study Eye (TG-MV-006, TG-MV-007 and Integrated Studies: Full Analysis Set)



Source: Figure 2 of the Applicant's Clinical Overview

Due to protocol violations there were 4 patients (1 placebo, 3 ocriplasmin) in the FAS group and 2 patients (1 placebo, 1 ocriplasmin) in the modified FAS groups who underwent vitrectomy prior to day 28. By the end of the study 28.3% (28/99) placebo patients and 19.8% (41/207) ocriplasmin patients underwent vitrectomy.

Secondary Efficacy Endpoint

- Proportion of subjects with total PVD at Day 28, as determined by masked Investigator assessment of B-scan ultrasound

Exploratory Endpoints

- Proportion of subjects not requiring vitrectomy
- Proportion of full-thickness macular holes (FTMHs) that closed without vitrectomy as determined by CRC
- Achievement of ≥2 and ≥3 lines improvement in best corrected visual acuity (BCVA) without need for vitrectomy
- Improvement in BCVA
- Improvement in the National Eye Institute (NEI) 25-Item Visual Function Questionnaire(VFQ-25)

Efficacy Results for Secondary and Exploratory Endpoints (TG-MV-006, TG-MV-007 and Integrated Studies)

TG-MV-006				**TG-MV-007**			
Placebo n/N (%)	**Ocriplasmin n/N (%)**	**Difference (95% CI)[a]**	**p-value[b]**	**Placebo n/N (%)**	**Ocriplasmin n/N (%)**	**Difference (95% CI)[a]**	**p-value[b]**
Proportion of Patients with Total PVD at Day 28							
7/107 (6.5)	36/219 (16.4)	9.9 (3.1, 16.7)	0.014	0/81 (0)	26/245 (10.6)	10.6 (6.8, 14.5)	< 0.001
Proportion of Patients with FTMH at Baseline who achieved Non-Surgical FTMH Closure at Day 28							
4/32 (12.5)	25/57 (43.9)	31.4 (14.1, 48.6)	0.002	1/15 (6.7)	18/49 (36.7)	30.1 (11.6, 48.5)	0.028
Proportion of Patients with FTMH at Baseline who achieved Non-Surgical FTMH Closure at Month 6							
5/32 (15.6)	26/57 (45.6)	30.0 (11.9, 48.0)	0.005	3/15 (20.0)	17/49 (34.7)	14.7 (−9.5, 38.9)	0.354
Proportion of Patients who received a Vitrectomy by Month 6							
31/107 (29.0)	45/219 (20.5)	−8.4 (−18.5, 1.7)	0.096	19/81 (23.5)	37/245 (15.1)	−8.4 (−18.6, 1.9)	0.091
Proportion of Patients with Non-Surgical ≥ 2-line Improvement in BCVA at Month 6							
12/107 (11.2)	56/219 (25.6)	14.4 (6.0, 22.7)	0.002	9/81 (11.1)	54/245 (22.0)	10.9 (2.3, 19.5)	0.035
Proportion of Patients with Non-Surgical ≥ 3-line Improvement in BCVA at Month 6							
7/107 (6.5)	23/219 (10.5)	4.0 (−2.2, 10.2)	0.310	0/81	22/245 (9.0)	9.0 (5.4, 12.6)	0.002

Source: Table 5 of the Applicant's Clinical Overview

Per the Appicant's submission "The primary endpoint comparison was performed with an alpha level of 0.05 as treatment efficacy was characterized by a single primary efficacy endpoint between 2 treatment groups." The formal statistical testing of the key secondary efficacy endpoint (total PVD) was to be evaluated only if statistical significance ($p<0.05$) was achieved in the analysis of the primary efficacy endpoint for 2 of the 3 predefined study populations (i.e. Full Analysis Set and Modified Full Analysis Set). ***Analyses of the remaining secondary endpoints were considered supportive or exploratory.*** *No prespecified statistical plan was in place to determine statistical significance of these endpoints. The results of those endpoints were described with nominal 95% CIs and nominal p-values without any statistical significance statements.*

There were a total of six predefined exploratory endpoints (note: BCVA was tested at ≥2 and ≥ 3 lines) proposed in the phase 3 studies. In addition to the predefined exploratory endpoints, the applicant also evaluated FTMH closure at two timepoints. Based on a conservative Bonferroni correction for multiplicity, the p-value would need to be approximately ***0.007*** *to* ***0.008*** *to be statistically significant. None of the exploratory endpoints demonstrate replicated efficacy in the two phase 3 trials.*

Visual Acuity

Although the categorical improvement from baseline of BCVA at Month 6 seems to favor the ocriplasmin treated group, it is observed that in study TG-MV-006, more patients in the ocriplasmin treated group had ≥ 2-line or 3-line ***worsening*** *in BCVA compared with the placebo group at Month 6 (as seen in the following table). In Study TG-MV-006, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was much higher in the ocriplasmin treated group compared with the placebo group (7.3% versus 1.9%, respectively) with a treatment difference of 5.4% and 95% CI of (1.1%, 9.7%). And in the combined analysis, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was also higher in the ocriplasmin treated group compared with the placebo group (5.6% versus 3.2%, respectively) with a treatment difference of 2.4% and 95% CI of (-0.9%, 5.7%).*

Categorical Improvement from Baseline in BCVA at Month 6, Irrespective of Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis; FAS, LOCF)

Time Point	TG-MV-006				TG-MV-007				Combined Analysis			
	Placebo (n=107) n (%)	Ocriplasmin (n=219) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (n=81)[c] n (%)	Ocriplasmin (n=245) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (N=188)[c] n (%)	Ocriplasmin (N=464) n (%)	Difference (95% CI)[a]	*P* value[b]
≥2-line Improvement in BCVA												
Month 6	18 (16.8)	66 (30.1)	13.3 (4.0, 22.7)	0.010	14 (17.5)	64 (26.1)	8.6 (-1.4, 18.6)	0.133	32 (17.1)	130 (28.0)	10.9 (4.1, 17.7)	0.003
≥3-line Improvement in BCVA												
Month 6	9 (8.4)	28 (12.8)	4.4 (-2.5, 11.2)	0.270	3 (3.8)	29 (11.8)	8.1 (2.3, 13.9)	0.049	12 (6.4)	57 (12.3)	5.9 (1.3, 10.5)	0.024
≥2-line Worsening in BCVA												
Month 6	5 (4.7)	22 (10.0)	5.4 (-0.3,11.0)	0.133	6 (7.5)	14 (5.7)	-1.8 (-8.2, 4.7)	0.594	11 (5.9)	36 (7.8)	1.9 (-2.3, 6.0)	0.352
≥3-line Worsening in BCVA												
Month 6	2 (1.9)	16 (7.3)	5.4 (1.1, 9.7)	0.067	4 (5.0)	10 (4.1)	-0.9 (-6.3, 4.5)	0.753	6 (3.2)	26 (5.6)	2.4 (-0.9, 5.7)	0.180

[a] The difference is the absolute difference and CIs between treatment groups are based on the normal approximation.

[b] p-value from Fisher's Exact test for each individual study; and P-value from CMH test for combined analysis, stratified by study.

[c] One patient did not have baseline BCVA measurement in Study TG-MV-007; therefore, the denominator in this analysis is 80 for placebo group, and 187 for the combined analysis.

Source: Table 14 of the Applicant's AC briefing package.

The following table shows categorical worsening from baseline in BCVA at Month 6 for patients with or without vitrectomy in each individual study and the combined analysis.

In Study TG-MV-006, for patients with vitrectomy, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was again much higher in the ocriplasmin treated group compared with the placebo group (20.0% versus 6.5%, respectively) with a treatment difference of 13.5% and 95% CI of (-1.0%, 28.1%); for patients without vitrectomy, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was still higher in the ocriplasmin treated group compared with the placebo group (4.0% versus 0.0%, respectively) with a treatment difference of 4.0% and 95% CI of (-1.1%, 6.9%).

In the combined analysis, for patients with vitrectomy, the proportion of patients with a ≥3 lines (15 letters) worsening in the visual acuity was also higher in the ocriplasmin treated group compared with the placebo group (15.9% versus 6.1%, respectively) with a treatment difference of 9.7% and 95% CI of (-0.6%, 20.1%)

Categorical Worsening from Baseline in BCVA at Month 6 with or without Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis; FAS, LOCF)

With Vitrectomy												
Time Point	TG-MV-006				TG-MV-007				Combined Analysis			
	Placebo (n=31) n (%)	Ocriplasmin (n=45) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (n=19)[c] n (%)	Ocriplasmin (n=37) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (N=50)[c] n (%)	Ocriplasmin (N=82) n (%)	Difference (95% CI)[a]	*P* value[b]
≥2-line Worsening in BCVA												
Month 6	3 (9.7)	10 (22.2)	12.5 (-3.5, 28.5)	0.219	3 (16.7)	5 (13.5)	-3.2 (-23.6, 17.3)	>0.999	6 (12.2)	15 (18.3)	6.0 (-6.4, 18.5)	0.347
≥3-line Worsening in BCVA												
Month 6	2 (6.5)	9 (20.0)	13.5 (-1.0, 28.1)	0.183	1 (5.6)	4 (10.8)	5.3 (-9.3, 19.8)	>0.999	3 (6.1)	13 (15.9)	9.7 (-0.6, 20.1)	0.087
Without Vitrectomy												
Time Point	TG-MV-006				TG-MV-007				Combined Analysis			
	Placebo (n=76) n (%)	Ocriplasmin (n=174) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (n=62) n (%)	Ocriplasmin (n=208) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (N=138) n (%)	Ocriplasmin (N=382) n (%)	Difference (95% CI)[a]	*P* value[b]
≥2-line Worsening in BCVA												
Month 6	2 (2.6)	12 (6.9)	4.3 (-4.3, 9.5)	0.239	3 (4.8)	9 (4.3)	-0.5 (-6.5, 5.5)	>0.999	5 (3.6)	21 (5.5)	2.0 (-2.0, 6.0)	0.134
≥3-line Worsening in BCVA												
Month 6	0 (0.0)	7 (4.0)	4.0 (-1.1, 6.9)	0.105	3 (4.8)	6 (2.9)	-2.0 (-7.8, 3.9)	0.433	3 (2.2)	13 (3.4)	1.2 (-2.0, 4.3)	0.191

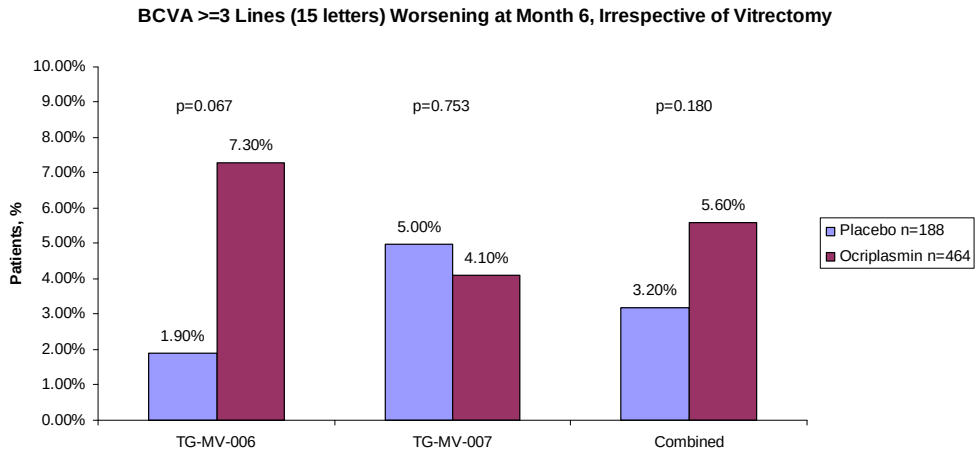
[a] The difference is the absolute difference and CIs between treatment groups are based on the normal approximation.

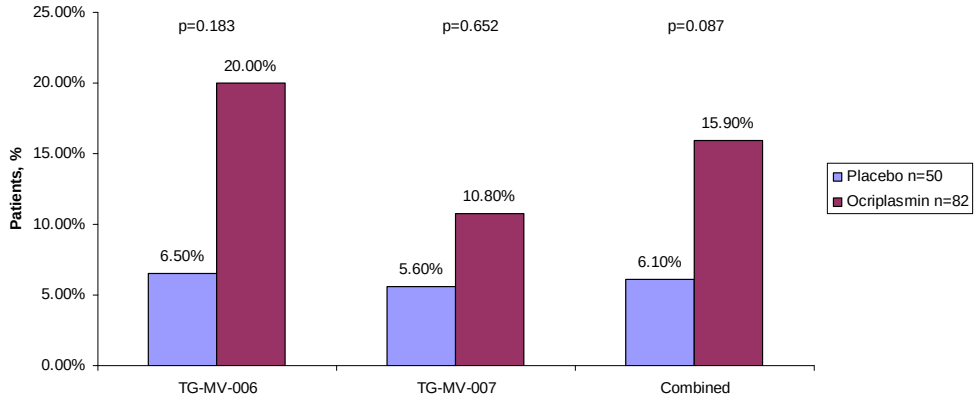
[b] p-value from Fisher's Exact test for each individual study; and P-value from CMH test for combined analysis, stratified by study.

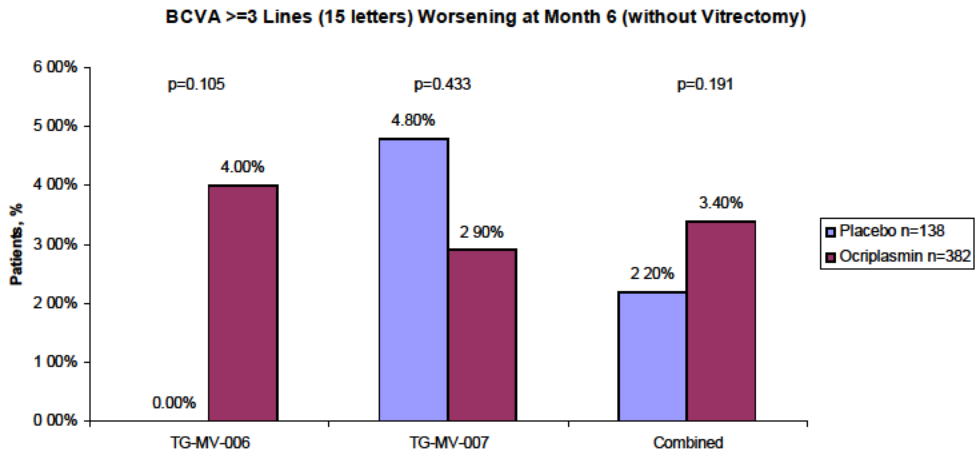
[c] One patient did not have baseline BCVA measurement in Study TG-MV-007; therefore, the denominator in this analysis is 18 for placebo group, and 49 for the combined analysis.

Source: Table 2.6.15 of the Applicant's Integrated Summary of Efficacy and the FDA statistical reviewer's own analysis.

The following graphs show the proportion of patients with a ≥3 lines (15 letters) worsening in BCVA at Month 6 for all patients, for patients with vitrectomy, and for patients without vitrectomy in each individual study and the combined analysis.

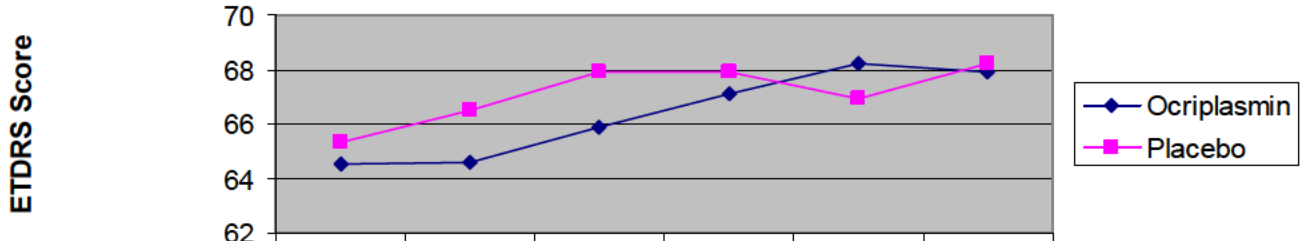






Compared to placebo treated patients, more ocriplasmin treated patients had worsening of BCVA as well as improvement of BCVA at Month 6; consequently, there was no difference between the ocriplasmin group and the placebo group in the change from baseline of BCVA at Month 6. As shown in the following graphs, the mean BCVA at Month 6 were similar for both the ocriplasmin and placebo groups in study TG-MV-006 (ocriplasmin vs. placebo: 67.9 vs. 68.2 letters) and study TG-MV-007 (ocriplasmin vs. placebo: 67.1 vs. 66.8 letters)

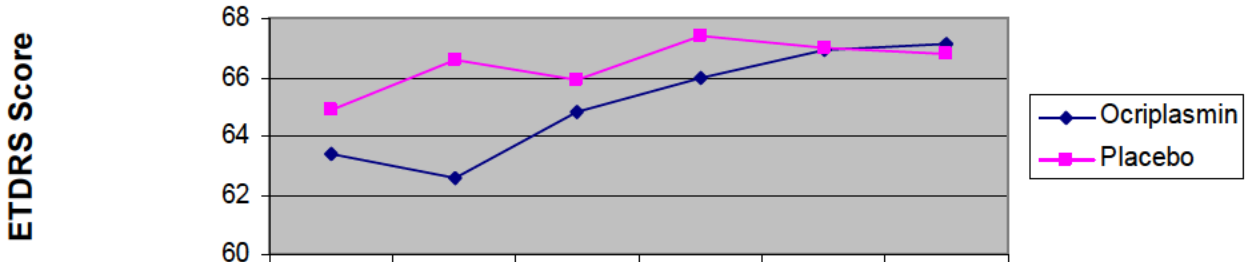
Mean Visual Acuity - Study 006 (FAS-LOCF)



	baseline	day 7	day 14	day 28	month 3	month 6
Ocriplasmin	64.5	64.6	65.9	67.1	68.2	67.9
Placebo	65.3	66.5	67.9	67.9	66.9	68.2

*FAS-LOCF – full analysis set with missing data imputed using LOCF
Source: Table 14.2.5.1 of the Applicant's Clinical Study Report TG-MV-006

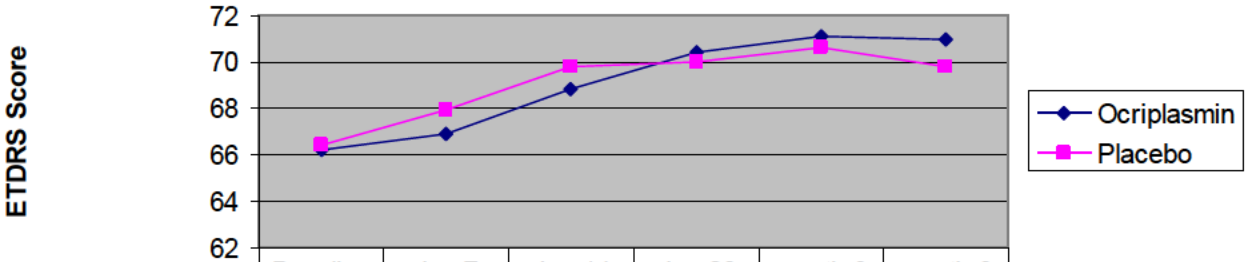
Mean Visual Acuity - Study 007 (FAS-LOCF)



	baseline	day 7	day 14	day 28	month 3	month 6
Ocriplasmin	63.4	62.6	64.8	66	66.9	67.1
Placebo	64.9	66.6	65.9	67.4	67	66.8

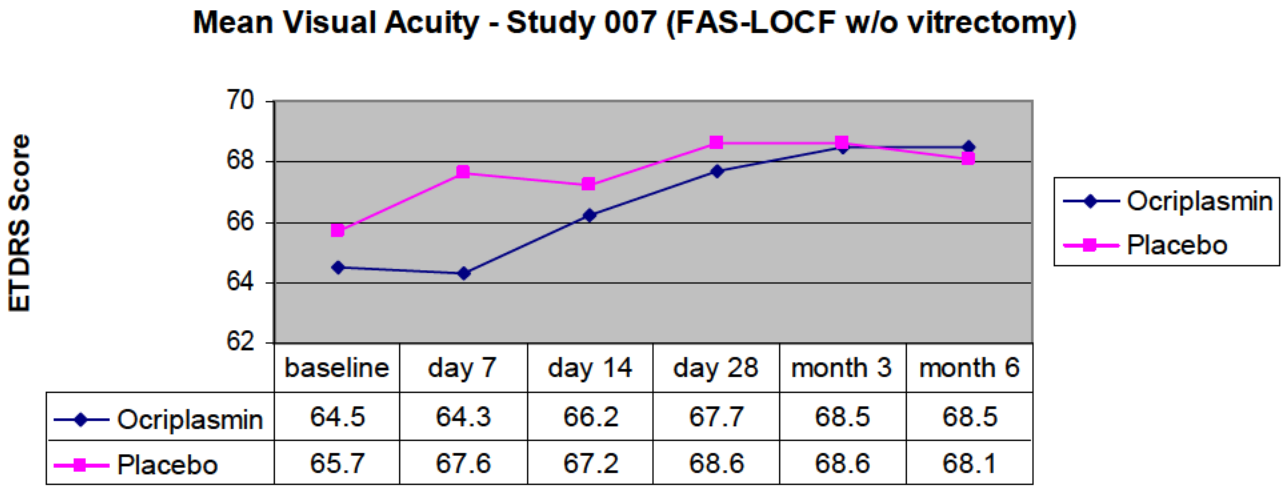
*FAS-LOCF – full analysis set with missing data imputed using LOCF
Source: Table 14.2.5.1 of the Applicant's Clinical Study Report TG-MV-007

Mean Visual Acuity - Study 006 (FAS-LOCF w/o Vitrectomy)



	Baseline	day 7	day 14	day 28	month 3	month 6
Ocriplasmin	66.2	66.9	68.8	70.4	71.1	71
Placebo	66.4	67.9	69.8	70	70.6	69.8

*FAS-LOCF – full analysis set with missing data imputed using LOCF
Source: Table 14.2.5.3 of the Applicant's Clinical Study Report TG-MV-006



	baseline	day 7	day 14	day 28	month 3	month 6
Ocriplasmin	64.5	64.3	66.2	67.7	68.5	68.5
Placebo	65.7	67.6	67.2	68.6	68.6	68.1

*FAS-LOCF – full analysis set with missing data imputed using LOCF
Source: Table 14.2.5.3 of the Applicant's Clinical Study Report TG-MV-007

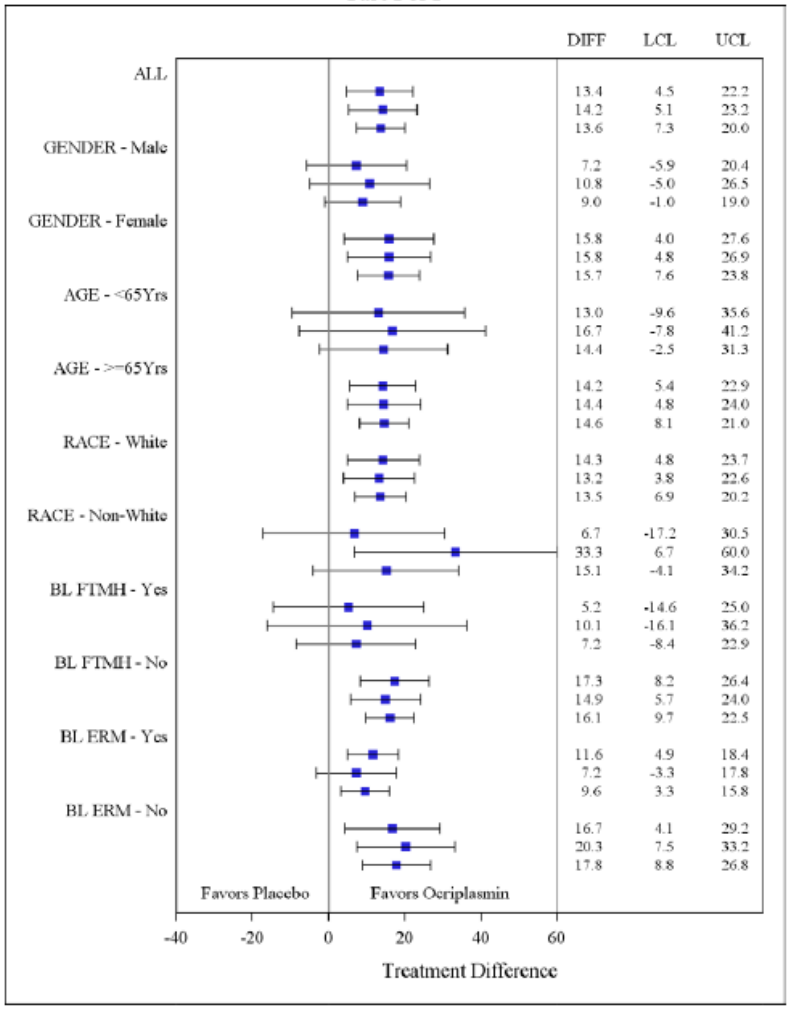
Subpopulations

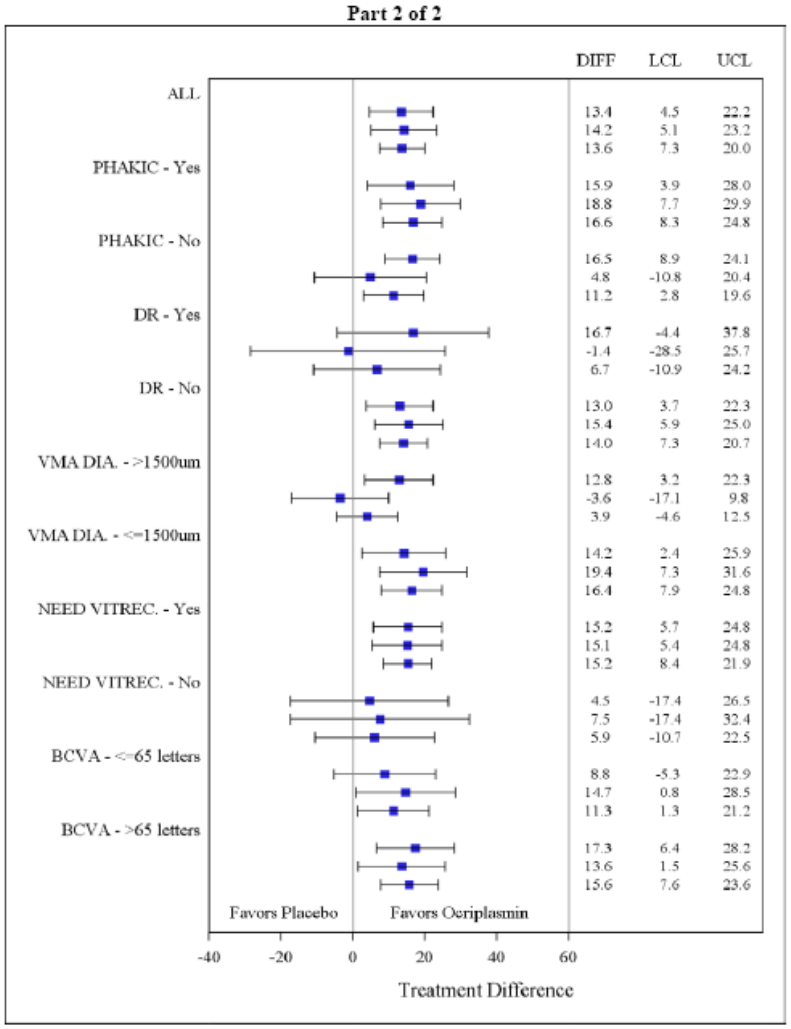
The following subgroups (Baseline demographics and ocular characteristics) were evaluated:

- Gender (male vs. female)
- Age (≤ 65 vs. > 65)
- Race (white vs. non-white)
- Baseline FTMH
- Baseline ERM
- Lens status (phakic versus pseudophakic)
- Baseline Diabetic Retinopathy
- Type of VMA (>1500µm versus ≤1500µm diameter)
- Baseline BCVA subgroups (>65 letters versus ≤65 letters).

Forest Plot for the Treatment Difference in the Proportion of Patients with VMA Resolution in the Study Eye at Month 6 without Creation of an Anatomical Defect (TG-MV-006, TG-MV-007 and Integrated Studies - Full Analysis Set)

Part 1 of 2





Source: Table 1.11.3 of the Applicant's Efficacy Information Amendment

Overall the results for these subgroups were consistent with the primary analysis results.

Safety Summary

Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study	Ocriplasmin						Placebo	Sham	No Treatment
	25µg	50µg	75µg	125µg	175µg	Any Dose			
TG-MV-001	30	10	11	9	0	60	0	0	0
TG-MV-003	29	0	33	32	0	94	31	0	0
TG-MV-010	0	0	0	34	0	34	0	0	4
Subtotal[a]	*59*	*10*	*44*	*75*	*0*	*188*	*31*	*0*	*4*
TG-MV-002	8	0	15	15	0	38	0	13	0
TG-MV-004	0	0	12	27	11	50	0	12	0
TG-MV-006	0	0	0	220	0	220	106	0	0
TG-MV-007	0	0	0	245	0	245	81	0	0
Subtotal[b]	*8*	*0*	*27*	*507*	*11*	*553*	*187*	*25*	*0*
Total	**67**	**10**	**71**	**582**	**11**	**741**	**218**	**25**	**4**

Source: Table 6 of the Applicant's Clinical Overview

[a] Subtotal for pre-planned vitrectomy studies

[b] Subtotal for studies without pre-planned vitrectomy

Demographic and Baseline Characteristics (Safety Set)

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo (N=187)		Ocriplasmin 125µg (N=465)		Control[a] N=247		Ocriplasmin Any Dose (N=741)	
Gender [n (%)]								
Male	73	(39.0%)	150	(32.3%)	98	(39.7%)	259	(35.0%)
Female	114	(61.0%)	315	(67.7%)	149	(60.3%)	482	(65.0%)
Race [n(%)]								
White	173	(92.5%)	429	(92.3%)	228	(92.3%)	633	(85.4%)[b]
Black	6	(3.2%)	23	(4.9%)	9	(3.6%)	29	(3.9%)
Asian	4	(2.1%)	8	(1.7%)	5	(2.0%)	13	(1.8%)
Other	4	(2.1%)	5	(1.1%)	5	(2.0%)	6	(0.8%)
Geographic region [n (%)]								
United States	142	(75.9%)	331	(71.2%)	173	(70.0%)	425	(57.4%)
Europe	45	(24.1%)	134	(28.8%)	74	(30.0%)	316	(42.6%)
BMI [n (%)]								
< 25	69	(36.9%)	148	(31.8%)	88	(35.6%)	223	(30.1%)
≥ 25	118	(63.1%)	314	(67.5%)	155	(62.8%)	479	(64.6%)
Age (years) at Baseline								
n	187		465		247		741	
Mean (SD)	70.7	(10.39)	72.0	(8.94)	70.0	(10.32)	70.0	(9.56)
Median	71.0		72.0		70.0		70.0	
Min - Max	24-97		18-93		24-97		18-93	
Age Group [n (%)]								
<65 years	42	(22.5%)	81	(17.4%)	60	(24.3%)	190	(25.6%)
≥ 65 years	145	(77.5%)	384	(82.6%)	187	(75.7%)	551	(74.4%)
<75 years	114	(61.0%)	273	(58.7%)	160	(64.8%)	494	(66.7%)
≥ 75 years	73	(39.0%)	192	(41.3%)	87	(35.2%)	247	(33.3%)

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo (N=187)		Ocriplasmin 125µg (N=465)		Control N=247		Ocriplasmin Any Dose (N=741)	
Baseline Diagnosis [n (%)][c]								
Full thickness macular hole[d]								
Yes	47	(25.1%)	105	(22.6%)	48	(19.4%)	114	(15.4%)
No	133	(71.1%)	332	(71.4%)	136	(55.1%)	356	(48.0%)
Unknown / not collected	7	(3.7%)	28	(6.0%)	63	(25.5%)	271	(36.6%)
Diabetic retinopathy								
Yes	15	(8.0%)	31	(6.7%)	29	(11.7%)	78	(10.5%)
No	172	(92.0%)	434	(93.3%)	218	(88.3%)	663	(89.5%)
Epiretinal membrane[e]								
Yes	67	(35.8%)	183	(39.4%)	68	(27.5%)	189	(25.5%)
No	119	(63.6%)	267	(57.4%)	122	(49.4%)	294	(39.7%)
Unknown / not collected	1	(0.5%)	15	(3.2%)	57	(23.1%)	258	(34.8%)
Lens status[f]								
Phakia	134	(71.7%)	293	(63.0%)	153	(61.9%)	363	(49.0%)
Pseudophakia	53	(28.3%)	172	(37.0%)	59	(23.9%)	190	(25.6%)
Not characterized	0		0		35	(14.2%)	188	(25.4%)
Vitrectomy expected if no improvement [n (%)][g]								
Yes	151	(80.7%)	397	(85.4%)				
No	36	(19.3%)	67	(14.4%)				

[a] Patients allocated to placebo, sham injection, or no treatment.
[b] Race was not recorded in TG-MV-001; therefore, race is missing for 60 (8.1%) patients.
[c] Patients may be included in multiple baseline diagnosis categories as appropriate.
[d] FTMH status at Baseline was recorded only for TG-MV-002, TG-MV-004, TG-MV-006 and TG-MV-007.
[e] ERM status at Baseline was recorded only for TG-MV-002, TG-MV-004, TG-MV-006 and TG-MV-007.
[f] Lens status was characterized for all studies except TG-MV-001, TG-MV-003 and TG-MV-010.
[g] Yes / no answer for the question asked of the investigator prior to randomization: "If no improvement in this patient's condition, do you think you would proceed to vitrectomy?" Recorded for TG-MV-006 and TG-MV-007 only.

Source: Table 6.of the Applicant's Summary of Clinical Safety

Major Safety Results

Deaths

Treatment	Study / Patient Number	Age (y)	Gender	Race	Injection Date	Date of Death	AE Resulting in Death (MedDRA Preferred Term)
Sham injection	TG-MV-002 / 011301	74	male	white	10-Dec-2008	(b) (6)	Cardiac arrest
Sham injection	TG-MV-002 / 081102	82	male	white	30-Mar-2007		Intestinal obstruction
Ocriplasmin 75µg	TG-MV-003 / 101021	75	male	white	21-Mar-2008		Myocardial infarction
Ocriplasmin 125µg	TG-MV-006 / 603008	81	female	white	22-Apr-2009		Cerebral hemorrhage
Ocriplasmin 125µg	TG-MV-006 / 622012	84	female	white	08-May-2009		Lung neoplasm malignant
Ocriplasmin 125µg	TG-MV-006 / 632008	83	female	white	22-Jul-2009		Cardiac failure congestive
Ocriplasmin 125µg	TG-MV-007 / 721008	76	female	white	16-Sep-2009		Brain cancer metastatic
Ocriplasmin 125µg	TG-MV-007 / 775003	88	female	white	11-Jun-2009		Lung neoplasm malignant

Source: Table 26.of the Applicant's Summary of Clinical Safety and the FDA statistical reviewer's own analysis.

For the pivotal placebo-controlled studies (TG-MV-006 and TG-MV-007), the death rate for placebo was 0/187 (0.0%); and the death rate for ocriplasmin (125 µg) was 5/465 (1.1%).

Overall, for all the studies combined, 8 deaths occurred during the clinical development program: 6/741 (0.8%) ocriplasmin-treated patients and 2/247 (0.8%) placebo or sham controlled patients.

Nonfatal Serious Adverse Events

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control[a] N=247		Ocriplasmin Any Dose N=741	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Number of ocular SAEs	20	(10.7%)	37	(8.0%)	22	(8.9%)	59	(8.0%)
Study eye	20	(10.7%)	36	(7.7%)	22	(8.9%)	57	(7.7%)
Non-study eye	0		2	(0.4%)	0		3	(0.4%)
Study eye SAEs by Preferred Term								
Macular hole	16	(8.6%)	24	(5.2%)	16	(6.5%)	35	(4.7%)
Vitreous adhesions	1	(0.5%)	5	(1.1%)	2	(0.8%)	5	(0.7%)
Visual acuity reduced	1	(0.5%)	3	(0.6%)	1	(0.4%)	3	(0.4%)
Retinal detachment	3	(1.6%)	2	(0.4%)	3	(1.2%)	4	(0.5%)
Eye inflammation	0		1	(0.2%)	0		1	(0.1%)
Hyphema	0		1	(0.2%)	1	(0.4%)	1	(0.1%)
Posterior capsule opacification	0		1	(0.2%)	0		2	(0.3%)
Vitreous hemorrhage	0		1	(0.2%)	1	(0.4%)	1	(0.1%)
Macular edema	1	(0.5%)	0		1	(0.4%)	1	(0.1%)
Cataract	0		0		0		3	(0.4%)
Optic disc vascular disorder	0		0		0		1	(0.1%)
Retinal artery occlusion	0		0		0		1	(0.1%)
Retinal vein occlusion	0		0		0		1	(0.1%)
Intraocular pressure increased	0		0		0		1	(0.1%)
Anterior chamber inflammation	0		0		0		1	(0.1%)
Choroidal detachment	0		0		0		1	(0.1%)
Macular degeneration	0		0		0		1	(0.1%)
Retinal tear	0		0		0		1	(0.1%)
Cataract traumatic	0		0		0		1	(0.1%)
Choroidal hemorrhage	0		0		1	(0.4%)	0	

[a] Patients allocated to placebo, sham injection or no treatment.
Source: Table 27 of the Applicant's Summary of Clinical Safety.

There are no significant differences in the rate of serious non-fatal adverse events between ocriplasmin and placebo.

Dropouts and/or Discontinuations

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control[a] N=247		Ocriplasmin Any Dose N=741	
	n	(%)	n	(%)	n	(%)	n	(%)
Safety set	187	(100.0%)	465	(100.0%)	247	(100.0%)	741	(100.0%)
Completed study	171	(91.4%)	436	(93.8%)	228	(92.3%)	701	(94.6%)
Discontinued from study	16	(8.6%)	29	(6.2%)	19	(7.7%)	40	(5.4%)
Reasons for discontinuation								
Adverse event	2	(1.1%)	4[b]	(0.9%)	2	(0.8%)	7[c]	(0.9%)
Investigator decision	1	(0.5%)	0		1	(0.4%)	0	
Withdrew consent	8	(4.3%)	13	(2.8%)	9	(3.6%)	17	(2.3%)
Lost to follow-up	5	(2.7%)	8	(1.7%)	5	(2.0%)	10	(1.3%)
Death[d]	0		4	(0.9%)	2	(0.8%)	5	(0.7%)
Other	0		0		0		1	(0.1%)

Source: Table 5 of the Applicant's Summary of Clinical Safety

[a] Patients allocated to placebo, sham injection, or no treatment

[b] Patient 721008 discontinued the study due to an AE (metastatic brain cancer, unrelated to ocriplasmin) and subsequently died due to this condition more than 30 days after study discontinuation and is therefore counted in this table in the "Adverse event" row rather than the "Death" row.

[c] In the clinical database and in Tables 1.1.2 and 1.1.3, the reason for discontinuation was reported as "Other" for Patient 001304 and as "Investigator decision" for Patient 002406. After reviewing these cases, the Sponsor concluded that "Adverse event" was a more appropriate reason for discontinuation for these patients. Therefore, each patient is counted in the "Adverse event" row rather than the "Investigator decision" and "Other" rows.

[d] Deaths were due to non-ocular AEs and were considered unrelated to study drug.

Patients with Adverse Events Leading to Study Withdrawal (Safety Set)

Treatment	Study / Patient Number	Age (y)	Gender	Race	Injection Date	Last Study Visit Attended by Patient	AE Leading to Withdrawal
Placebo	TG-MV-006/601002	64	male	white	06JAN2009	Month 3	spondylolisthesis
Placebo	TG-MV-006/638003	64	female	black	15JUN2009	Month 3	cataract subcapsular
Ocriplasmin 25µg[a]	TG-MV-001/001304	61	male	unknown[b]	21NOV2005	Day 90	recurrent retinal detachment
Ocriplasmin 50µg[c]	TG-MV-001/002406	82	male	unknown[b]	09MAR2006	Day 3	pancreatic carcinoma
Ocriplasmin 75µg	TG-MV-003/108014	69	female	white	25MAR2008	Day 90	macular oedema
							retinal depigmentation
							vitreous inflammation
Ocriplasmin 125µg	TG-MV-006/603007	62	female	white	14APR2009	Month 3	breast cancer
Ocriplasmin 125µg	TG-MV-006/627008	65	female	white	26AUG2009	Month 3	pancreatic carcinoma
Ocriplasmin 125µg	TG-MV-007/721008	76	female	white	16SEP2009	Day 7	brain cancer metastatic
Ocriplasmin 125µg	TG-MV-007/774004	65	female	white	05NOV2009	Month 3	breast cancer

Source: Table 29 of the Applicant's Summary of Clinical Safety

a In the clinical database, the reason for withdrawal is reported as "Other".

b Race was not recorded in TG-MV-001

c In the clinical database, the reason for withdrawal was reported as "Investigator decision".

In review of the cases of adverse events that led to study withdrawal, the majority were due to existing systemic medical conditions. There are no significant differences in the rate of study withdrawal due to adverse events between ocriplasmin and placebo.

Common Adverse Events

Adverse Events Reported at a Rate of ≥ 1% for Patients Treated with Ocriplasmin 125µg in the Placebo-Controlled Studies (Safety Set)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control[1] N=247		Ocriplasmin Any Dose N=741	
Number of adverse events	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any event	129	(69.0%)	356	(76.6%)	180	(72.9%)	593	(80.0%)
Any non-ocular event	53	(28.3%)	140	(30.1%)	82	(33.2%)	255	(34.4%)
Any ocular event	106	(56.7%)	324	(69.7%)	149	(60.3%)	538	(72.6%)
Study eye event	99	(52.9%)	317	(68.2%)	141	(57.1%)	529	(71.4%)
Non-study eye event	22	(11.8%)	61	(13.1%)	29	(11.7%)	101	(13.6%)
Eye disorders								
Any event	101	(54.0%)	321	(69.0%)	142	(57.5%)	518	(69.9%)
Study eye event	95	(50.8%)	314	(67.5%)	135	(54.7%)	510	(68.8%)
Non-study eye event	20	(10.7%)	57	(12.3%)	26	(10.5%)	90	(12.1%)
Ocular AEs[2]								
Vitreous floaters	16	(8.6%)	82	(17.6%)	20	(8.1%)	123	(16.6%)
Conjunctival haemorrhage	24	(12.8%)	68	(14.6%)	49	(19.8%)	129	(17.4%)
Eye pain	11	(5.9%)	62	(13.3%)	19	(7.7%)	91	(12.3%)
Photopsia	5	(2.7%)	56	(12.0%)	7	(2.8%)	67	(9.0%)
Vision blurred	8	(4.3%)	41	(8.8%)	9	(3.6%)	50	(6.7%)
Macular hole	19	(10.2%)	36	(7.7%)	20	(8.1%)	56	(7.6%)
Visual acuity reduced	9	(4.8%)	30	(6.5%)	9	(3.6%)	42	(5.7%)
Visual impairment[3]	3	(1.6%)	26	(5.6%)	3	(1.2%)	28	(3.8%)
Retinal oedema	2	(1.1%)	25	(5.4%)	2	(0.8%)	32	(4.3%)
Macular oedema	3	(1.6%)	19	(4.1%)	10	(4.0%)	45	(6.1%)
Intraocular pressure increased	10	(5.3%)	18	(3.9%)	17	(6.9%)	65	(8.8%)
Anterior chamber cell	5	(2.7%)	17	(3.7%)	12	(4.9%)	57	(7.7%)
Photophobia[4]	0		17	(3.7%)	0		25	(3.4%)
Vitreous detachment	3	(1.6%)	13	(2.8%)	3	(1.2%)	14	(1.9%)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control N=247		Ocriplasmin Any Dose N=741	
Ocular discomfort	2	(1.1%)	13	(2.8%)	4	(1.6%)	17	(2.3%)
Iritis	1	(0.5%)	13	(2.8%)	1	(0.4%)	13	(1.8%)
Cataract	8	(4.3%)	12	(2.6%)	12	(4.9%)	39	(5.3%)
Dry eye	2	(1.1%)	11	(2.4%)	3	(1.2%)	14	(1.9%)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control N=247		Ocriplasmin Any Dose N=741	
Metamorphopsia	1	(0.5%)	11	(2.4%)	1	(0.4%)	15	(2.0%)
Conjunctival hyperaemia	4	(2.1%)	10	(2.2%)	6	(2.4%)	25	(3.4%)
Vitreous adhesions	2	(1.1%)	10	(2.2%)	3	(1.2%)	13	(1.8%)
Retinal degeneration	1	(0.5%)	10	(2.2%)	1	(0.4%)	13	(1.8%)
Eye irritation	6	(3.2%)	9	(1.9%)	9	(3.6%)	19	(2.6%)
Maculopathy	4	(2.1%)	9	(1.9%)	9	(3.6%)	25	(3.4%)
Eye pruritus	3	(1.6%)	9	(1.9%)	3	(1.2%)	25	(3.4%)
Foreign body sensation in eyes	3	(1.6%)	9	(1.9%)	6	(2.4%)	16	(2.2%)
Punctate keratitis	2	(1.1%)	9	(1.9%)	2	(0.8%)	10	(1.3%)
Conjunctival oedema	5	(2.7%)	8	(1.7%)	6	(2.4%)	13	(1.8%)
Retinal haemorrhage	4	(2.1%)	8	(1.7%)	11	(4.5%)	29	(3.9%)
Blepharitis	2	(1.1%)	8	(1.7%)	3	(1.2%)	13	(1.8%)
Conjunctival bleb	2	(1.1%)	8	(1.7%)	2	(0.8%)	9	(1.2%)
Retinal pigment epitheliopathy	0		8	(1.7%)	4	(1.6%)	25	(3.4%)
Lacrimation increased	2	(1.1%)	7	(1.5%)	4	(1.6%)	14	(1.9%)
Eyelid oedema	1	(0.5%)	7	(1.5%)	8	(3.2%)	22	(3.0%)
Retinal tear	5	(2.7%)	6	(1.3%)	7	(2.8%)	25	(3.4%)
Conjunctivitis	2	(1.1%)	6	(1.3%)	3	(1.2%)	8	(1.1%)
Anterior chamber flare	2	(1.1%)	6	(1.3%)	8	(3.2%)	32	(4.3%)
Macular degeneration	2	(1.1%)	6	(1.3%)	2	(0.8%)	13	(1.8%)
Cataract nuclear	4	(2.1%)	5	(1.1%)	12	(4.9%)	29	(3.9%)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control N=247		Ocriplasmin Any Dose N=741	
Ocular hyperaemia	1	(0.5%)	5	(1.1%)	1	(0.4%)	15	(2.0%)
Scotoma	0		5	(1.1%)	0		5	(0.7%)
Miosis	0		5	(1.1%)	0		5	(0.7%)
Corneal abrasion	0		5	(1.1%)	1	(0.4%)	7	(0.9%)
Vitreous haemorrhage	3	(1.6%)	4	(0.9%)	6	(2.4%)	15	(2.0%)
Posterior capsule opacification	3	(1.6%)	4	(0.9%)	5	(2.0%)	10	(1.3%)
Retinal detachment	3	(1.6%)	4	(0.9%)	4	(1.6%)	11	(1.5%)
Macular cyst	2	(1.1%)	4	(0.9%)	2	(0.8%)	4	(0.5%)
Cataract cortical	3	(1.6%)	3	(0.6%)	5	(2.0%)	5	(0.7%)
Corneal disorder	3	(1.6%)	3	(0.6%)	3	(1.2%)	7	(0.9%)
Corneal erosion	2	(1.1%)	3	(0.6%)	3	(1.2%)	6	(0.8%)
Eyelid ptosis	2	(1.1%)	1	(0.2%)	3	(1.2%)	2	(0.3%)
Vitreous opacities	2	(1.1%)	1	(0.2%)	3	(1.2%)	2	(0.3%)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control N=247		Ocriplasmin Any Dose N=741	
Vitritis	0		2	(0.4%)	2	(0.8%)	13	(1.8%)
Cataract subcapsular	0		0		2	(0.8%)	8	(1.1%)
Corneal oedema	0		0		3	(1.2%)	5	(0.7%)
Non-Ocular AEs								
Bronchitis	3	(1.6%)	13	(2.8%)	5	(2.0%)	16	(2.2%)
Headache	4	(2.1%)	12	(2.6%)	11	(4.5%)	32	(4.3%)
Nausea	1	(0.5%)	12	(2.6%)	3	(1.2%)	22	(3.0%)
Nasopharyngitis	5	(2.7%)	9	(1.9%)	9	(3.6%)	21	(2.8%)
Upper respiratory tract infection	2	(1.1%)	7	(1.5%)	3	(1.2%)	10	(1.3%)
Urinary tract infection	2	(1.1%)	7	(1.5%)	4	(1.6%)	7	(0.9%)
Dyspnoea	1	(0.5%)	7	(1.5%)	1	(0.4%)	9	(1.2%)
Back pain	1	(0.5%)	6	(1.3%)	1	(0.4%)	8	(1.1%)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control N=247		Ocriplasmin Any Dose N=741	
Influenza	2	(1.1%)	5	(1.1%)	3	(1.2%)	14	(1.9%)
Arthralgia	2	(1.1%)	3	(0.6%)	2	(0.8%)	3	(0.4%)
Oropharyngeal pain	2	(1.1%)	3	(0.6%)	2	(0.8%)	4	(0.5%)
Sinusitis	3	(1.6%)	2	(0.4%)	4	(1.6%)	7	(0.9%)
Constipation	2	(1.1%)	2	(0.4%)	3	(1.2%)	3	(0.4%)
Toothache	2	(1.1%)	2	(0.4%)	2	(0.8%)	2	(0.3%)
Vomiting	2	(1.1%)	2	(0.4%)	2	(0.8%)	5	(0.7%)
Insomnia	2	(1.1%)	2	(0.4%)	4	(1.6%)	4	(0.5%)
Pneumonia	2	(1.1%)	1	(0.2%)	3	(1.2%)	2	(0.3%)
Pyrexia	2	(1.1%)	1	(0.2%)	2	(0.8%)	1	(0.1%)
Anaemia	2	(1.1%)	1	(0.2%)	2	(0.8%)	1	(0.1%)
Muscle strain	2	(1.1%)	0		2	(0.8%)	0	
Gout	2	(1.1%)	0		2	(0.8%)	0	

[(1)]Patients allocated to placebo, sham-injection or no treatment.
[(2)]Includes study eye and non-study eye AEs.
[(3)]The verbatim term entopic phenomena (as can occur in setting of PVD) was conservatively coded to the preferred term (PT) visual impairment instead of floaters/photopsia in the appendix tables and in-text tables.
[(4)]Two reports of photosensitivity (Patient 602-001 and Patient 602-005, Study TG-MV-006) that occurred in the study eye were coded to the preferred term Photosensitivity reaction. These events may represent 2 additional reports of photophobia.
Source: Table 1.11.3 of the Applicant's Efficacy Information Amendment

Adverse events in the above table are listed in order of frequency seen in the ocriplasmin groups with those events highlighted that occur at a rate of ≥ 2 times the rate of the placebo group.

While several adverse events seen are consistent with the known adverse events associated with intraocular injections, many occur at a much higher rate in the ocriplasmin group which may suggest a drug related effect in addition to the background rate. These events include eye pain, ocular discomfort, iritis. In addition there are several adverse events which occur at a much higher rate in ocriplasmin treated patients which raise concerns about the drugs potential effect on the retina. Photopsia, blurred vision, visual impairment, retinal edema, macular edema, metamorphopsia and retinal degeneration occur at a rate of 2-4 times more in the ocriplasmin group versus placebo. Photopsia is known to occur during release of traction and may be the result of a higher incidence of adhesions in the drug group. The visual acuity data discussed previously in the efficacy section would possibly suggest that these adverse events may be transient and cause no long term harm to the retina; however, this conclusion can not be made definitively based on the data available.

Discussion Points for the Advisory Committee:

1. Has substantial evidence been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of vitreomacular adhesions?

2. Has substantial evidence been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of macular holes associated with vitreomacular adhesions?

3. Has substantial evidence been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of all macular holes regardless of the presence of adhesions?

4. Are additional studies needed prior to approval to evaluate the safety of ocriplasmin's effect on the retina? If so, what studies?

5. Do the benefits of administering ocriplasmin for the treatment of vitreomacular adhesions outweigh the potential risks.

6. If this product is approved, are there any suggestions concerning labeling for this product?